Perioperative myocardial ischemic injury in high-risk vascular surgery patients: Incidence and clinical significance in a prospective clinical trial

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Objective: **The purpose of this study was to assess prospectively the incidence, health care resource utilization, and economic burden associated with perioperative myocardial ischemic injury (PMII) in high-risk patients undergoing noncardiac vascular surgery.**

Methods: **Two hundred thirty-six patients consented to participate in a pharmacoeconomic substudy as part of a randomized, multicenter clinical trial. Patients were assessed for myocardial ischemic injury by using clinical, biochemical, and electrocardiographic criteria. PMII was defined as fatal or nonfatal myocardial infarction, new or worsened congestive heart failure, or new arrhythmias. Resource utilization parameters were compared for patients with and without PMII. Patients underwent the following index procedures: open abdominal aortic aneurysm repair (n = 44), bypass for aortoiliac disease (n = 29), bypass for femoropopliteal disease (n = 62), bypass for femorotibial disease (n = 71), extra-anatomic bypass (n = 23), and miscellaneous (n = 7). Patients undergoing carotid endarterectomy or only endovascular interventions were excluded. The incremental cost of PMII was estimated by applying the average costs (adjusted to 2004 US dollars) of the hospital ward ($700.00/d) or intensive care unit ($2500.00/d) to the length of stay differences for patients with and without PMII.**

Results: **The overall mortality was 3.4% (8/236), and 7 of 8 deaths were related to PMII. PMII occurred in 42 (17.8%) of 236 patients: 22 myocardial infarctions, 11 congestive heart failures, and 12 new arrhythmias (3 patients had 2 PMII events). There was no evidence of differences in the incidence of PMII among the various index procedures. PMII was associated with a dramatic increase in resource utilization. The mean length of stay was 16.8 and 10.0 days for patients with and without PMII, respectively ($P < .001$). Intensive care unit care was required by 35 (83.3%) of 42 patients with and 121 (62.4%) of 194 patients without PMII ($P < .009$). The mean intensive care unit length of stay was 6.6 and 3.7 days for patients with and without PMII, respectively ($P < .009$). Ten (23.8%) of 42 patients with and 20 (10.3%) of 194 patients without PMII returned to the emergency department for care after discharge ($P < .02$).**

Conclusions: **In modern vascular surgery practice, PMII remains common despite the availability of β-blockers and other preventative strategies. PMII is associated with dramatic increases in resource utilization and cost. The increase in resource utilization associated with PMII resulted in an estimated incremental cost per patient of $9980.00. If 250,000 high-risk open vascular operations are performed annually in the United States, the economic burden of PMII in these procedures alone approximates $444 million. Strategies to decrease PMII incidence and severity should be evaluated in large-scale prospective trials. (J Vasc Surg 2006;43:533-8.)**

In the United States, nearly 25 million patients undergo noncardiac surgical procedures each year. More than 8 million of these patients have coronary artery disease or risk factors for coronary artery disease, and approximately 1 million patients experience perioperative cardiac morbidity or cardiac-related mortality.[1-4] In the highest-risk group are more than 500,000 patients undergoing noncardiac vascular surgery. The prevalence of coronary disease in these patients and the hemodynamic stress often associated with vascular surgery accounts for their observed high risk of perioperative myocardial ischemic events.[5-7]

Perioperative myocardial ischemic injury (PMII) is a marker for coronary artery disease–associated morbidity and mortality.[3] PMII can aggravate pre-existing cardiac conditions or result in myocardial infarction (MI), unstable angina, ventricular arrhythmia, congestive heart failure (CHF), or sudden cardiac death during the period between the surgical procedure and hospital discharge. Furthermore, it seems intuitively obvious that PMII should increase the resource utilization and cost associated with vascular surgery. Estimates from the 1980s suggested that the in-hospital economic burden of PMII for all noncardiac operations was more than $12 billion annually.[4] Because of the aging of our population and the ever-rising costs of health care, the economic burden associated with PMII is of great interest to private and government health care insurance providers.

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Despite the prevalence of PMII and its likely economic effect, little is known about incremental PMII associated resource utilization and cost. The spectrum of PMII runs from clinically inapparent troponin leaks through major transmural infarction or sudden cardiac death. Because catastrophic perioperative events are unusual, it is tempting for individual practitioners, who may see only one such event per year, to ignore or downplay the significance of PMII in their practice. The occasional subendocardial infarct, CHF episode, or rhythm disturbance may escape the careful scrutiny of vascular surgeons, anesthesiologists, and their quality-assurance departments. The primary objective of this economic study was to measure prospectively the incidence, resource utilization, and associated economic burden of PMII in patients undergoing high-risk noncardiac vascular surgery in the United States.

METHODS

The study from which the patients for this pharmacoeconomic (PE) substudy were recruited was a phase II international randomized double-blind multicenter placebo-controlled trial that examined the effects of Zoniporide compared with placebo.[8] Zoniporide is a sodium hydrogen ion exchange inhibitor that in animal models has been shown to decrease myocardial injury related to ischemia-reperfusion events when compared with placebo. In phase I trials, the agent was proven safe for administration to humans.

The inclusion criteria defined a noncardiac vascular surgery population at high risk of PMII events.[8] Eligibility criteria included the following:

1. Age 18 years or older.
2. Open major vascular surgery (aortic or aortoiliofemoral reconstruction for aneurysm or occlusive disease, extra-anatomic bypass for aortoiliac disease, femoral reconstruction, and femoropopliteal or tibial bypass).
3. Either (1) a history of three or more of the following: age 70 years or older, documented stroke, prior MI, medically managed coronary artery disease with active angina pectoris (Canadian class ≥II), diabetes mellitus, CHF (New York Heart Association class ≥II), or symptomatic cardiac arrhythmia or (2) a history of one of these risk factors and radionuclide/echocardiographic and electrocardiographic evidence of reversible ischemia in response to exercise or pharmacologic stress.

The cardiac stress study must have been performed within the previous year, and complete revascularization must not have occurred before surgery. Subjects undergoing emergency vascular procedures with risk factors, as described previously, were also eligible if study procedures could be followed and not delay the operation. Patients undergoing carotid endarterectomy or endovascular surgical procedures were excluded.[8]

At each participating institution, the study protocol and consent form were approved by the institutional review board. Participation in the trial was contingent upon the patient's meeting eligibility criteria and consenting to participate. An additional approved consent form was required for participation in this PE substudy. The 236 patients participating represent all US subjects in the main clinical trial who also consented to participate in this substudy.

Table I. Distribution of index procedures

Procedure	*n*
Open abdominal aortic aneurysm repair	44
Bypass for aortoiliac disease	29
Bypass for femoropopliteal disease	62
Bypass for femorotibial disease	71
Extra-anatomic bypass	23
Miscellaneous (eg, femoral endarterectomy)	7

Table II. Demographic characteristics for US patients participating in the PE substudy

Variable	*PE substudy (n = 236)*
Sex	
Male	160 (67.8%)
Female	76 (32.2%)
Age, n (%)	
<65 y	63 (26.7%)
65-74 y	86 (36.6%)
75-84 y	77 (32.6%)
≥85 y	10 (4.2%)
Mean age (y)	69.98
SD (y)	10.40
Range (y)	28-96
Race	
White	208 (88.1%)
Black	22 (9.3%)
Asian	0 (0.00%)
Other	6 (2.5%)

PE, Pharmacoeconomic.

The primary goal of the study was to compare the zoniporide- and placebo-treated groups with respect to the occurrence of cardiac end points (fatal or nonfatal MI, new or progressive CHF, or serious cardiac arrhythmia) within 30 days of operation, as defined by an independent end point classification committee that used routine surveillance by cardiac biomarkers, electrocardiograms, and symptoms.

As part of the clinical trial, this PE substudy was conducted in parallel to assess resource utilization through postoperative day 30. All PE data were collected on clinical trial case report forms that included overall hospital length of stay, intensive care unit (ICU) length of stay, procedures, rehospitalizations, emergency department visits, physician visits, and other resource utilization parameters. The clinical results within the primary zoniporide study found no differences in the rates of cardiac events between the treatment and placebo groups; thus, data were pooled to perform resource utilization analysis to allow comparison between patients with and without PMII. To simplify the analysis of resource utilization and cost, only patients hospitalized in the US study sites were included in this analysis.

Table III. All-cause mortality and PMII-related events overall and by index procedure

Event	*Overall*	*AAA*	*Afem*	*Fempop*	*Femtib*	*ExtrA*	*Misc*
Death	8 (3.4%)	2 (4.6%)	1 (3.5%)	2 (3.2%)	2 (2.8%)	1 (4.4%)	0
PMII death	7 (3.0%)	1 (2.3%)	1 (3.5%)	2 (3.2%)	2 (2.8%)	1 (4.0%)	0
PMII overall	42 (17.8%)	9 (20.5%)	7 (24.1%)	8 (12.9%)	14 (19.7%)	4 (17.4%)	0
MI (nonfatal)	22 (9.3%)	5 (11.4%)	4 (13.8%)	4 (6.5%)	7 (9.9%)	2 (8.7%)	0
CHF	11 (4.7%)	2 (4.6%)	3 (10.3%)	1 (1.6%)	4 (5.6%)	1 (4.4%)	0
ARH	12 (5.1%)	3 (6.8%)	2 (6.9%)	3 (4.8%)	3 (4.2%)	1 (4.4%)	0

MI, CHF, arrhythmia, and death were not mutually exclusive. There were three patients who experienced two PMII events.
AAA, Abdominal aortic aneurysm repair; *Afem,* aortoiliofemoral reconstructions for occlusive disease; *Fempop,* reconstructions for femoropopliteal disease; *Femtib,* reconstructions for femorotibial disease; *ExtrA,* extra-anatomic reconstructions for aortoiliac disease; *PMII,* perioperative myocardial ischemic injury; *MI,* myocardial infarction; *CHF,* new or worsened congestive heart failure; *ARH,* new cardiac arrhythmia; *Misc,* miscellaneous.

Table IV. Index hospitalization length of stay data through day 30 by the presence of a PMII event

		PMII event		
Resource utilization item	*Overall PE substudy (n = 236)*	*Yes (n = 42)*	*No (n = 194)*	P *value*
No. patients still hospitalized from index operation at day 30	9 (3.8%)	6 (14.3%)	3 (1.6%)	<.001
Mean length of index stay, d (SD)	11.2 (7.4)	16.8 (8.9)	10.0 (6.4)	<.001
No. patients requiring ICU stay during index hospitalization	156 (66.1%)	35 (83.3%)	121 (62.4%)	<.009
Mean ICU length of stay during index hospitalization, d (SD)	4.4 (4.6)	6.6 (6.3)	3.7 (3.7)	<.009

PMII, Perioperative myocardial ischemic injury; *PE,* pharmacoeconomic; *ICU,* intensive care unit.

To estimate the incremental cost of PMII events, the average cost of a hospital day on a general ward was estimated to be $700 according to a national cost-of-living index reflecting a national average of 314 cities ($645 in 2002 adjusted to 2004 dollars).[9] The cost of an ICU day was assumed to be $2500 on the basis of current literature and national hospital statistics.[10,11] By using these cost data and the incremental total and ICU lengths of stay associated with PMII events in our study, we estimated the cost associated with PMII events.

Descriptive statistics were performed to compare and contrast significant differences in resource utilization by the presence of PMII events through day 30 after surgery. Descriptive statistics including the mean, median, standard deviation, and range collectively provided an interpretation of the distributional characteristics of the data. The degree and type of missing data were explored and documented. Frequencies of missing data were assessed overall and stratified by treatment group, and χ^2 tests were used to determine whether the rate of the missing data varied widely across the treatment groups at either baseline or day 30. Analysis of variance *P* values and χ^2 tests of association were reported for resource use; however, the nonparametric Wilcoxon test was also performed for certain continuous variables in resource use, such as length of stay and ICU stay. Nonparametric tests such as the Wilcoxon test were used if the assumption of normality was untenable. For categorical variables, the analyses were conducted via χ^2 tests of association. Statistical significance was inferred for $P < .05$.

RESULTS

Of the 370 patients enrolled in US sites for the trial, 236 (69%) also participated in the PE substudy. The distribution of index procedures performed in these patients is shown in Table I. The patient demographics for the substudy are shown in Table II. Differences in the distribution of race, age, and index procedures were similar (no significant differences) across treatment groups in both the entire clinical trial and the sample used for the substudy.

Table III summarizes the procedure-specific and overall perioperative (30-day) clinical event rates for the PE substudy. The 30-day all-cause mortality rate was 8 (3.4%) of 236, and 7 of 8 deaths (3.0% of the study cohort) were related to PMII. The 30-day rate of clinical PMII events (fatal and nonfatal) was 17.8% (42 patients experienced 45 events). There were no significant differences in the proportions of patients who experienced clinical events between the overall clinical study and the PE substudy group. There were no significant differences in the incidence of PMII events when placebo-treated patients were compared with patients treated with each of the zoniporide dosing regimens.[8] In the patients receiving zoniporide, the incidence of PMII events was 16.3%, compared with 15.7% in the placebo group ($P > .5$). In addition, there were no significant differences in the mortality and PMII morbidity rates among the different index procedures (Table III). For this reason, the resource utilization data from the placebo and treatment groups and from the various index procedures have been pooled.

The effect of PMII events was seen primarily during the hospitalization for the index vascular procedure (Table IV). The experience of a PMII event was a significant predictor of increased resource utilization as measured by hospital length of stay and ICU stay. Patients who experienced a PMII event stayed approximately 7 days longer in the hospital and approximately 3 days longer in the ICU than

Table V. ER visits and rehospitalization through day 30 by the presence of a PMII event

Resource utilization item	*Overall PE substudy (n = 236)*	*PMII event*		P *value*
		Yes (n = 42)	*No (n = 194)*	
No. patients requiring an ER visit after discharge from index hospital stay	30 (12.7%)	10 (23.8%)	20 (10.3%)	<.02
Mean number of ER visits	0.13 (0.33)	0.24 (0.43)	0.10 (0.30)	NS
No. patients requiring rehospitalization for any reason	28 (11.9%)	6 (14.3%)	22 (11.3%)	NS
Length of revisit, d (SD)	6.9 (4.7)	4.3 (2.9)	7.4 (4.8)	NS
No. patients requiring ICU stay during rehospitalization for any reason	6 (2.5%)	3 (7.1%)	3 (1.6%)	<.04
ICU stay, d (SD)	2.3 (0.3)	3 (1.7)	1.7 (1.2)	NS
Number (%) of patients requiring rehospitalization for vascular problems	12 (5.1%)	0 (0%)	12 (6.2%)	.10
Length of revisit, d (SD)	9.1 (5.2)	—	9.1 (5.2)	—
No. patients requiring rehospitalization for cardiac problems	3 (1.3%)	1 (2.4%)	2 (1.0%)	.48
Length of revisit, d (SD)	4.3 (1.2)	5	4 (1.4)	.67

PMII, Perioperative myocardial ischemic injury; *PE,* pharmacoeconomic; *ER*, emergency room; *ICU,* intensive care unit; *NS,* not significant.

Table VI. Incremental cost of a PMII event during the index hospital stay

Resource use	*No. days*	*Unit cost per day (2004 USD)*	*Total cost*
Subjects without a PMII event			
Index hospital days (total)	10	—	$13,660
Ward days	6.3	$700	$4410
ICU days	3.7	$2500	$9250
Subjects with a PMII event			
Index hospital days (total)	16.8	—	$23,640
Ward days	10.2	$700	$7140
ICU days	6.6	$2500	$16,500
Incremental cost of a PMII event			$9980

PMII, Perioperative myocardial ischemic injury; *USD,* US dollars; *ICU,* intensive care unit.

those without a PMII event. In addition, patients with a PMII event were four times more likely to still be hospitalized at day 30.

Hospital follow-up data are shown in Table V. Patients who had a PMII event were twice as likely to require an emergency room visit after discharge from the index procedure and were more than four times as likely to require ICU care if rehospitalized.

Table VI describes the key incremental costs associated with PMII events. The incremental cost of a PMII event in this PE substudy is conservatively estimated at $9980 per event. Given the fatal and nonfatal PMII event rate of 17.8% in this trial, the total cost of PMII in this study was estimated at approximately $419,000. Using the incremental cost and event rates from the trial, the cost of PMII events projected on a national basis is $444 million annually, assuming that half (250,000) of the more than 500,000 patients undergoing open surgical procedures meet high-risk criteria.

A significant number of missing data were noted for data collected on discharge status, activities of daily living, and work loss. For the one third of the PE substudy population that answered these questions, approximately 34% were discharged to a skilled nursing facility, 22% to an acute rehabilitation center, 20% to a subacute or postacute rehabilitation center, 3% to an intermediate care facility, 12% to home with assistance (half paid/half unpaid care), and 1.5% to home without assistance. For assistance with activities of daily living after hospital discharge, 73% required assistance with housekeeping, 33% with leisure activities, 78% with preparing meals, 81% with transportation, and 54% with self-care. The work-loss questions were typically not answered; only 14 patients reported being unable to do their paid or volunteer work after hospital discharge. Because of the missing data and concern as to whether the data would be representative of the entire PE substudy, the effect of PMII events on these areas was not assessed.

DISCUSSION

This study is the only large multicenter prospective trial measuring the incidence of and resource utilization associated with cardiac complications of noncardiac vascular surgery. One older economic burden projection estimated that perioperative MI alone cost more than $500 million annually for patients undergoing all noncardiac operations (approximately $25 million annually in the United States).[1] Prospective systematic assessments of the burden of PMII events after noncardiac vascular surgery have not been reported previously.

Our cost results are in line with a recent publication by Fleisher et al,[12] who conducted a retrospective analysis of Medicare data in patients who underwent abdominal aortic aneurysm repair. The incremental charges associated with a

perioperative MI were $15,000 (approximately $11,250 in costs assuming a 0.75 cost-to-charge ratio). The incremental charges associated with a perioperative death were $21,909 (approximately $16,432 in costs). In our study, the incremental cost of a PMII event was estimated at almost $10,000 for a mix of aortic and more distal noncardiac vascular procedures. Not surprisingly, the key cost drivers identified in this study were hospital and ICU lengths of stay.

We conservatively estimate that the current cost of PMII events for the highest-risk patients undergoing noncardiac vascular procedures is more than $440 million annually in the United States. The implications of the burden of illness of PMII events for physicians, hospital decision-makers, and national policy-makers are substantial. Over the coming decades, the elderly population is expected to grow by 25% to 35%.[5] Projections suggest that the overall number of noncardiac surgical procedures will double in this age group (currently 6-8 million) to nearly 12 million annually.[5] It is in this elderly age group that there is the highest risk of PMII morbidity/mortality after surgery. Even if we assume PMII event rates as low as 5%, this would result in a staggering burden when considering the projected growth of vascular and general surgical procedures in the coming years.

Aggressive preoperative surgical and interventional management of coronary disease has been touted as a potentially effective means for managing perioperative cardiac risk.[7] The recent Coronary Artery Revascularization Prophylaxis trial, however, showed that preoperative surgical or catheter-based coronary revascularization was ineffective in preventing perioperative MI and in decreasing longer-term mortality in selected patients scheduled for noncardiac vascular surgery.[13] The rate of perioperative MI was 12% in the revascularization group and 14% in the nonrevascularization group ($P = .37$), and the mortality at a mean follow-up of 2.7 years was 22% in the no-revascularization group and 23% in the revascularization group ($P = .92$).[13] Although the highest-risk cardiac patients (left main stenosis >50%, ejection fraction <20%, and severe aortic stenosis) were excluded from the trial, the results do suggest that prophylactic coronary revascularization in most vascular surgery patients is unlikely to be effective in preventing PMII or its related mortality.[13]

On a more hopeful and positive note, β-blockers have been shown to be effective in the prevention of perioperative MI and cardiac-related mortality in patients undergoing open aneurysm repair.[14] In their very important study, Poldermans et al[14] selected a group of high-risk patients undergoing vascular surgery for randomization to standard perioperative care vs standard perioperative care plus bisoprolol. Perioperative cardiac death was 3.4% in the bisoprolol group and 17% in the control group ($P = .02$). Nonfatal MI occurred in none of the bisoprolol group and in 17% of the control group ($P < .001$).[14] Bisoprolol was, therefore, highly effective in preventing PMII in this study.

In a much larger survey of high-risk patients undergoing noncardiac surgery in the United States, Lindenauer et al[15] showed that perioperative β-blocker therapy was associated with reduced in-hospital mortality and that the protective effect of β-blockers increased with increasing cardiac risk. The dramatic effect of β-blockade in preventing PMII in these studies has spawned significant interest in other potential chemoprophylactic regimens using other β-blockers, antiplatelet agents, reductase inhibitors, and newer agents. In fact, the clinical trial from which our PE data were derived was a study of a new sodium hydrogen ion exchange inhibitor designed as a potential chemoprophylactic agent.[8] Given the failure of invasive measures to alter perioperative or long-term cardiac-related mortality in the Coronary Artery Revascularization Prophylaxis trial, large-scale chemoprophylactic trials must be performed to determine the optimal means for preventing PMII.

This study has several limitations, including the short 30-day follow-up, which likely resulted in an underestimation of the true economic burden of PMII events. Furthermore, missing data in the assessment of quality of life after discharge made analysis of the effect of PMII on posthospitalization quality of life, non–hospitalization-related economic burdens, and noneconomic burdens impossible. Another limitation is our lack of detailed data on perioperative medical therapy in the study cohort, which prevented an analysis of the effect of β-blockers and other medications on the incidence and resource intensity of PMII events. However, our substudy was designed to establish the incidence of and resource utilization associated with PMII in current vascular practice and not to assess the benefit of any particular regimen. The limited sample of patients who experienced PMII events (42 of 236 patients) prevented meaningful subanalyses of PMII for specific surgical procedures. Thus, we were unable to determine whether the overall findings of increased resource utilization after a PMII event hold equally true for each of the individual surgical procedures included in the trial. Increasing the sample size by analyzing the global data might have provided sufficient statistical power, although it would be difficult to apply global findings to specific countries or health care systems. In addition, our method of estimating cost by using resource utilization as reflected in length of stay and ICU utilization probably underestimates cost. Geographic and interinstitutional variations in charges and in cost-charge ratios made the use of individual hospital bills problematic and equally subject to error.

Our study differs from other studies of perioperative cardiac morbidity and mortality in our definition of cardiac morbidity and mortality. In many studies, fatal and nonfatal MI is the only end point. In this study we used a broader definition of PMII that included CHF and new significant arrhythmias along with infarction. By including these end points, which, although less precisely quantifiable, were adjudicated by an end point committee, we hoped to capture all PMII events likely to influence resource utilization and thereby achieve a more accurate assessment of PMII effects.

In conclusion, in current vascular practice, PMII remains common, affecting 17.8% of subjects in this prospective clinical trial. The occurrence of a PMII event in this

study was associated with dramatic increases in hospital length of stay, ICU utilization, postdischarge emergency ward visits, and cost. Strategies to decrease the incidence of PMII, such as chemoprophylactic regimens and the use of less invasive endovascular vascular interventions in high-risk patients, should be evaluated in large-scale prospective trials to determine the optimal means for preventing PMII and to determine their effect on costs and outcomes.

AUTHOR CONTRIBUTIONS

Conception and design: W.C.M, L.A.F, SH, SS, J.C.C, JS
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